EXHIBIT A

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of:	Zeldis	Confirmation No.:	1866
Serial No.:	10/699,110	Art Unit:	1612
Filed:	October 30, 2003	Examiner:	Fay, Zohreh A.
For:	METHODS FOR THE TREATMENT AND MANAGEMENT OF MACULAR DEGENERATION USING CYCLOPROPYL-N-{2-[(1S)-1-(3-ETHOXY-4-METHOXYPHENYL)-2-(METHYLSULFONYL)ETHYL]-3-OXOISOINDOLINE-4-YL}CARBOXAMIDE	Docket No: CAM:	9516-083-999 501872-999082

DECLARATION BY PETER H. SCHAFER, PH.D. UNDER 37 C.F.R. § 1.132

Mail Stop AF

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

I, PETER H. SCHAFER, Ph.D., declare as follows:

1. I have personal knowledge of the matters contained herein, or know them by my review of U.S. Application No. 10/699,110 or my review of studies performed at the Vanderbilt University School of Medicine, Departments of Pathology and Ophthalmology.

I. Background

2. I received my Bachelor of Science degree in Biological Chemistry from the University of Chicago, Chicago, Illinois in 1991. I received my Ph.D. degree from the Department of Biochemistry, Molecular Biology, and Cell Biology at Northwestern University, Evanston, Illinois in 1996.

3. From 1996 to 1999, I was a post-doctoral researcher at The R.W. Johnson Pharmaceutical Research Institute in Raritan, New Jersey. From 1999 to present, I have been employed by Celgene Corporation, Summit, New Jersey, as a Research Scientist, a Senior

Research Scientist, a Group Leader, then as an Associate Director of Biology. Currently, I hold a position of the Director of Biology in the Department of Drug Discovery at Celgene Corporation.

4. I have published in peer-reviewed journals and made presentations at various academic conferences. I am also a named co-inventor of several patents and patent applications, including applications and patents owned by Celgene Corporation.

5. I am affiliated with the International Society for the Biological Treatment of Cancer, American Association for the Advancement of Science, and American Association of Immunologists. I have been serving as a reviewer for academic journals such as the Journal of Pharmacology and Experimental Therapeutics, European Journal of Hematology, and Leukemia and Lymphoma. My curriculum vitae is attached hereto as **Exhibit A.**

II. Evaluation of cyclopropyl-N-{2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-3-oxoisoindoline-4-yl}carboxamide

6. On the basis of my review of U.S. Application No. 10/699,110, I understand that the pending claims in the present application recite, *inter alia*, methods of treating macular degeneration comprising administering cyclopropyl-N-{2-[(1S)-1-(3-ethoxy-4-methoxyphenyl)-2-(methylsulfonyl)ethyl]-3-oxoisoindoline-4-yl}carboxamide ("the instant compound").

7. I understand that Celgene Corporation commissioned the Vanderbilt University School of Medicine, Departments of Pathology and Ophthalmology, to evaluate the efficacy of the instant compound in the inhibition of choroidal neovascularization and to compare any such efficacy to Lucentis®, a FDA-approved drug for the treatment of wet age-related macular degeneration.

A. Protocol

8. I understand that the tests utilized the laser-induced rupture of Bruch's membrane choroidal neovascularization ("CNV") model. These tests were performed on both mice and rats. Specifically, the tests were performed on Brown Norway rats and C57BL/6J mice (males; 4-6 weeks of age).

9. I understand that laser-induced rupture of Bruch's membrane was used to generate CNV. The animals were anesthetized with xylazine hydrochloride (10 mg/kg) and ketamine (50 mg/kg), and the pupils were dilated with 1% tropicamide (Alcon Labs, Inc.; Fort Worth, TX). A hand-held cover slide was used as a contact lens, and an argon laser photocoagulator (532 nm) mounted on a slit-lamp (Coherent Novus Omni, Lumenis Inc.; Santa Clara, CA) was employed to create four burns centered around the optic nerve head in the retinal mid-periphery (50 μm spot size, 0.1 sec duration, 360 mW) in the rats. For the mice, the procedures were similar with the exception that the laser energy was set to 260 mW. This procedure causes a bubble at the time of laser application to indicate rupture of Bruch's membrane. Burns not resulting in a bubble were not included in the study. Immediately after laser treatment, the rats and mice were divided into four groups for the administration of drugs.

10. I understand that the dosing regime for the mice was as follows: (1) oral administration of the instant compound at 5 mg/kg BID; (2) oral administration of the instant compound at 15 mg/kg BID; (3) oral administration of the vehicle BID; and (4) intravitreal administration of 2 μL Lucentis® (10 mg/mL, positive control treatment) at 1, 3, and 7 days following laser treatment.

11. I understand that the dosing regime for the rats was as follows: (1) oral administration of the instant compound at 10 mg/kg BID; (2) oral administration of the instant compound at 25 mg/kg BID; (3) oral administration of the vehicle BID; and (4) intravitreal administration of 5 μL Lucentis® (10 mg/mL, positive control treatment) at 1, 3, and 7 days following laser treatment.

12. I understand that fourteen days following laser application, the rats and mice were sacrificed to measure the extent of CNV at the Bruch's membrane rupture sites. The eyes of the animals were removed, and choroid-sclera-retinal pigment epithelium flat-mounts were prepared by removing the cornea and lens in 10% phosphate-buffered formalin. After dissecting the retina from the eyecup and discarding it, radial cuts were made in all four quadrants in order to flatten the remaining tissue. The flattened choroid-sclera-retinal pigment epithelium tissue was then mounted in Gel Mount (Biomedia; Victoria, Australia). Choroidal neovascular growth was assessed at two weeks post-laser treatment in

fluorescently-stained flat-mounts, using published methods. *See, e.g.*, Bora *et al.*, *J. Immunol.* 2005, 174(1):491-7. Endothelial cells were identified using FITC-conjugated Griffonia simplicifolia isolectin B_4 (Sigmma-Aldrich, Inc.), and the elastin of the surrounding extracellular matrix was stained using donkey anti-elastin antibody conjugated to Cy3 (Santa Cruz Biotech., Inc.). Areas of abnormal vascular growth were measured via computer-assisted image analysis using high-resolution digital images of the stained choroid-sclera-retinal pigment epithelium flat-mounts. The effects of the various treatments on the progression of laser-induced CNV were determined using an analysis of variance (ANOVA) and the Dunnett's post-hoc test with significance set to $P<0.05$. The sizes of the four lesions were averaged for each eye, the two eyes were averaged for each animal, and the values derived from each animal were averaged for each treatment group. The treatment group averages were used for the final analysis.

B. Results

13. I understand that with regard to the tests on mice, oral administration of the instant compound resulted in significant inhibition of laser-induced CNV. Specifically, administration of the instant compound at 5 mg/kg BID resulted in a 69% reduction in the neovascular area, and the administration at 15 mg/kg resulted in a 73% reduction in the neovascular area ($P<0.002$). Moreover, the observed inhibition resulting from the administration of the instant compound was remarkably higher than the inhibition resulting from the intravitreal injection of Lucentis®, which was 36% ($P=0.0913$ under Dunnett's Method; $P=0.0423$ under Student's t-test). *See* **Exhibit B**, Figure 1.

14. I understand that with regard to the tests on rats, oral administration of the instant compound resulted in significant inhibition of laser-induced CNV. Specifically, administration of the instant compound at 10 mg/kg BID resulted in a 61% reduction in the neovascular area, and administration at 25 mg/kg BID resulted in a 65% reduction in the neovascular area ($P<0.0001$). Moreover, the observed inhibition resulting from the administration of the instant compound was comparable to the inhibition resulting from the intravitreal injection of Lucentis®, which was 62% ($P<0.0001$). *See* **Exhibit B** Figure 2.

III. Conclusion

15. It is my opinion that the observed efficacy of the instant compound in rat and mice tests is significant and surprising. Specifically, it is significant and surprising that oral administration of the instant compound performed as well as or better than the intravitreal injection of Lucentis®, which represents the current standard of clinical care in connection with the treatment of wet age-related macular degeneration.

16. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like may be punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of any patent issuing from the present application.

Dated: 5 August 2008

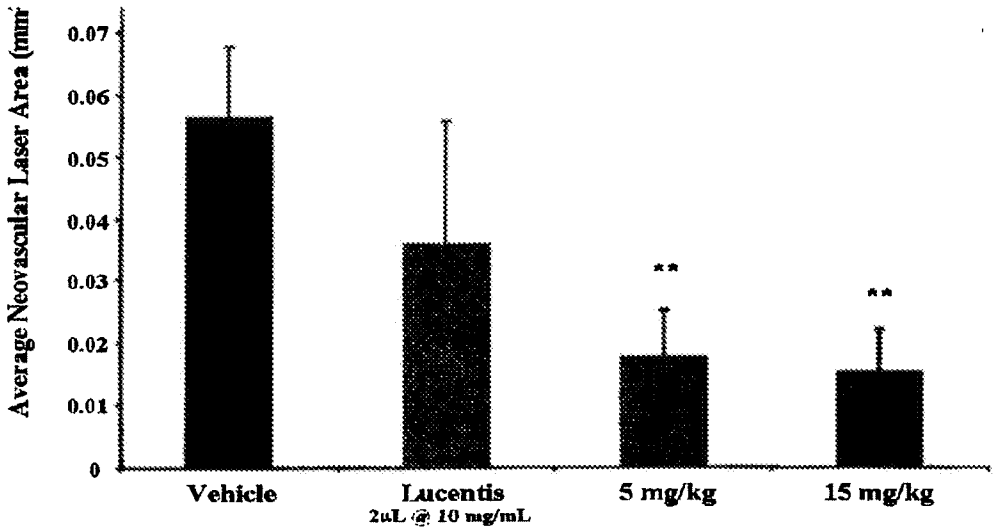
Peter H. Schafer

PETER H. SCHAFER, Ph.D.

EXHIBIT B

Figure 1

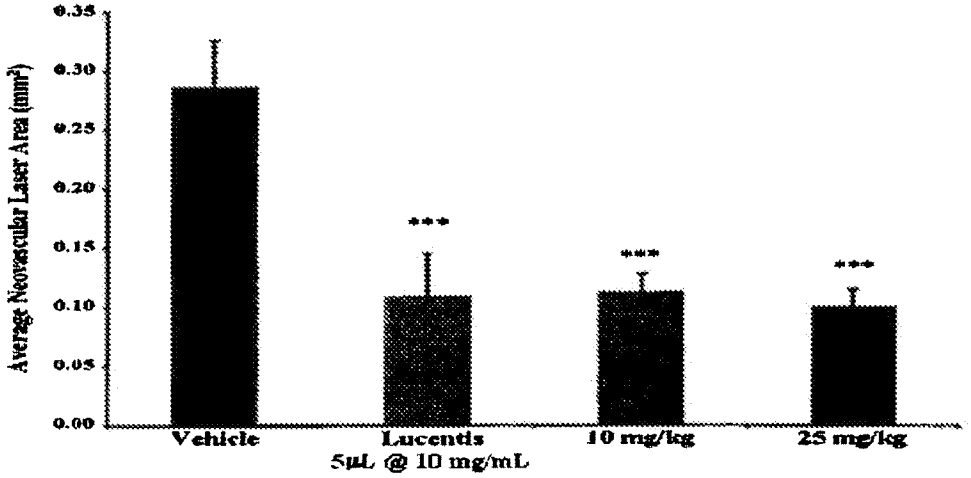
Histogram of Instant Compound on Laser-Induced Choroidal Neovascularization Areas in Mice



Asterisks (**) represent significance levels of P<0.002 vs. vehicle control.

Figure 2

Histogram o Instant Compound on Laser-Induced Choroidal Neovascularization Areas in Rats



Asterisks (**) represent significance levels of P<0.0001 vs. vehicle control.

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Curriculum Vitae

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BIOGRAPHICAL INFORMATION

Nationality: United States Citizen
Place of Birth: Chicago, IL

EDUCATION

Doctor of Philosophy (December 1996)
Department of Biochemistry, Molecular Biology, and Cell Biology
Northwestern University, Evanston, IL

Bachelor of Science (June 1991)
Biological Chemistry, University of Chicago, Chicago, IL

PROFESSIONAL EXPERIENCE & RESEARCH TRAINING

Director of Biology, Department of Drug Discovery (Nov. 2006-present)
Associate Director of Biology, Department of Drug Discovery (Sept. 2003-Nov. 2006)
Group Leader (Oct. 2001-Sept. 2003)
Senior Research Scientist (Jan 2001-Oct. 2001)
Research Scientist (Apr. 1999-Jan 2001)
Immunotherapeutics, Drug Discovery
Celgene Corporation, Warren, NJ, and Summit, NJ
Research: Project Leader for SelCIDs™ (Selective Cytokine Inhibitory Drugs, PDE4 Inhibitors); Mechanism of action studies on thalidomide and IMiDs™ (Immunomodulatory Drugs).

Postdoctoral Research Associate (John J. Siekierka, Ph.D.; Nov. 1996-Apr. 1999)
Immunosuppression Team, Drug Discovery Research, The R. W. Johnson Pharmaceutical Research Institute, Raritan, NJ
Research: p38 mitogen-activated protein kinase in CD28-mediated signaling and IL-4 production in T cells

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Graduate Research Assistant (Susan K. Pierce, Ph.D.; June 1992-Nov. 1996)
Department of Biochemistry, Molecular Biology, and Cell Biology, Northwestern University, Evanston, IL
Dissertation: The assembly, structure and regulation of function of MHC class II-antigenic peptide complexes

Research Assistant (Donald A. Rowley, M.D., Ph.D.; 1989-1991)
Committee on Immunology, Department of Pathology, University of Chicago, IL
Research: Transforming growth factor-β and tumor escape from immunosurveillance

PROFESSIONAL MEMBERSHIPS

International Society for the Biological Treatment of Cancer
American Association for the Advancement of Science
American Association of Immunologists
Reviewer, Journal of Pharmacology and Experimental Therapeutics
Reviewer, European Journal of Hematology
Reviewer, Leukemia and Lymphoma
Reviewer, Life Sciences

AWARDS

Thomas Alva Edison Patent award, from R&D Council of NJ, for *US6962940 B2,* (+)-2-[1-(3-ethoxy-4-methoxyphenyl)-2-methylsulfonylethyl]-4-acetylaminoisoindoline-1,3-dione:Methods of using and compositions thereof. November 7, 2007.
Revlimid® sNDA Multiple Myeloma Merit Award, June 29, 2006.
Thalomid® sNDA Multiple Myeloma Merit Award, May 25, 2006.
Revlimid® Contributor Functional Legacy Award, February 28, 2006.
National Research Service Award, Cell and Molecular Biology Training Grant, US Department of Health and Human Services, Public Health Service, September 1, 1993-August 31 1995.

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Gandhi, A.K., Schafer, P. H., Naziruddin, S., Parton, A., Verhelle, D., Brady, H., and Stirling, D.I. Lenalidomide Inhibits Proliferation of Chromosome 5 Mutant Hematopoietic Tumor Cells and Interferes with Adaptor Protein Complex Assembly and Phosphorylation. *International MDS Symposium*, Nagasaki, Japan, May 2005.

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